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头颈部肿瘤放疗后吞咽困难防治的研究现状

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【摘要】 吞咽困难是头颈部肿瘤放疗后常见的不良反应, 在接受放化疗的头颈部肿瘤患者中, 超过 76% 的患者会出现吞咽困难, 轻者降低生活质量, 重者可能危及生命。吞咽困难的形成与肿瘤分期、治疗方法和康复计划等相关, 其预防和治疗是保障头颈部肿瘤患者生活质量的关键, 但是目前临床防治措施明显不完善。笔者从吞咽系统的解剖及生理过程、放疗后头颈部肿瘤患者吞咽困难的形成原因、放疗对头颈部肿瘤患者吞咽困难发生发展过程的影响、吞咽困难的评估以及吞咽功能训练等方面进行综述, 以期进一步为头颈部肿瘤患者放疗后出现吞咽困难的防治提供思路。

【关键词】 头颈部肿瘤; 放射治疗剂量; 吞咽障碍; 生活质量

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Research status of prevention and treatment of dysphagia after radiotherapy for head and neck tumors

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【Abstract】 Dysphagia is the common adverse reaction after the radiotherapy for head and neck tumors. More than 76% of patients with head and neck cancer who received chemoradiotherapy had difficulty swallowing. The life quality of patients with mild dysphagia will be affected, while patients with severe symptoms may suffer from life danger. The existence of dysphagia is related to the tumor status, treatment methods, rehabilitation means and so on. Its prevention and treatment are the key to ensure the quality of life of patients with head and neck cancer. However, the current clinical prevention and treatment methods are obviously insufficient. This paper researches the anatomical and physiological process of swallowing system and the causes of the formation of dysphagia in head and neck tumors, and makes a review on the influence of radiotherapy on its developmental process, the evaluation of dysphagia and the prevention measures such as the training of swallowing functions in order to provide more thoughts on further preventing the appearance of dysphagia.

【Key words】 Head and neck neoplasms; Radiotherapy dosage; Deglutition disorders; Quality of life

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随着头颈部肿瘤发病率的升高以及发病渐趋年轻化, 以放疗和手术为基础的综合治疗有了快速的发展, 但是吞咽困难仍是头颈部肿瘤患者放疗后的常见并发症, 原发肿瘤位置(如喉或下咽)、侵犯范围、手术切除、放疗靶区及治疗剂量等多种因素共同导致吞咽困难的形成^[1]。头颈部肿

瘤放疗后的吞咽困难会导致患者出现营养不良、误吸、吸入性肺炎、焦虑等问题, 降低患者的生活质量, 甚至缩短其生存期^[2]。对于有较好预后且能长期生存(如人乳头状瘤病毒相关头颈部肿瘤等)的患者, 必须面对吞咽困难这一问题^[3]。笔者针对吞咽系统的解剖及生理过程、头颈部肿瘤患

者放疗后吞咽困难的形成原因、放疗对吞咽困难发生发展过程的影响、吞咽困难的评估以及吞咽功能训练等方面进行综述。

1 正常吞咽系统的解剖及生理过程

吞咽系统的解剖结构复杂,包括口腔、咽和喉。这些吞咽器官的共同作用是将食物从口腔输送到食道。这一过程涉及约50对肌肉和三叉神经、面神经、舌咽神经、迷走神经及舌下神经5对脑神经^[4]。Hedström等^[5]明确了对吞咽较为重要的吞咽困难-误吸相关结构,包括软腭、舌根、舌肌、咽缩肌、乳突舌肌、颊舌肌、舌骨舌肌、二腹肌、腮腺、下颌下腺、会厌、声门、声门上喉和食管括约肌。正常的吞咽过程包括自主的口腔阶段和自主的咽部与食道阶段:食物的咀嚼发生在口腔,需要唇、颊、下颌和舌头的协调运动;随着舌头推动食物进入咽部,喉前庭上方的会厌关闭,喉的抬高和声门的关闭阻止食物进入气道;咽部收缩肌的收缩以及下咽负压吸引和重力作用使食物进入食管^[4]。

2 吞咽困难的形成原因

2.1 吞咽系统破坏

14%~18%的患者可能因肿瘤压迫或侵犯吞咽结构出现治疗前吞咽障碍,基线功能障碍会增加慢性吞咽困难发生的风险^[6]。

手术破坏吞咽系统(如舌肌、咽缩肌、喉部等)是造成头颈部肿瘤患者吞咽困难的重要因素,术后是否会出现吞咽困难很大程度上取决于切除范围,如全喉切除术后患者吞咽困难的发生率高达60%,而接受术后放疗患者的吞咽困难发生风险是不接受放疗患者的2.4倍,且在术后3~12个月未接受放疗的患者的吞咽功能逐渐改善,而接受辅助放疗患者的未见改善^[7]。

约80%的头颈部肿瘤患者需要放疗,放疗联合化疗是头颈部肿瘤器官保留的标准治疗方法^[8]。联合放化疗与单纯放疗相比,患者的病死风险降低了19%,5年总体生存率提高了8%。但是,在接受放化疗的头颈部肿瘤患者中,超过76%的患者出现吞咽困难,其中根治性同步放化疗患者吞咽困难的发生率为60%^[6]。在头颈区域,吞咽系统与肿瘤位置临近,极易受到辐射损伤,之后舌根运动无力,咽部转运时间延长,喉部抬高水平降低,会厌运动能力减弱,吞咽功能缺乏协调性,从而导致吞咽困难。同时,多项研究结果显示,舌肌、咽缩肌、声门、声门上喉和食管括约肌受到的照射剂量与后期吞咽困难的发生密切相关,当上、中咽缩肌的平均辐射剂量高于60 Gy时,吞咽困难的发生率明显升高^[9-10]。其病理机制是放疗导致的纤维化致使肌肉

顺应性和收缩性变差,58%的头颈部肿瘤患者在放疗后1年观察到颈部纤维化,放疗后8年颈部纤维化的发生率升高至68%^[11]。但King等^[12]发现,照射后3个月肌纤维未发生变化时,肌肉活性已降低,如舌肌收缩速度减慢,这可能是微血管和肌蛋白损伤造成的,因此仅根据纤维化与否判断是否产生了吞咽困难可能会低估肌组织功能障碍的程度。

2.2 急性放射损伤

放疗导致的急性放射损伤是造成吞咽困难的重要因素,联合化疗会增加不良反应,如3级和4级黏膜炎,加重吞咽困难^[13]。放疗后4~5周,患者开始出现不同程度的黏膜炎和不良反应(如黏膜上皮脱落、黏膜及间质水肿),并可发生局部溃疡和坏死,由此导致的疼痛和食道狭窄造成的吞咽运动限制会引起急性吞咽困难^[13-14]。

不同放疗剂量的分割模式也会对急性放射损伤产生影响,Matuschek等^[15]发现,加速超分割放疗后急性黏膜炎的出现更早,其发生率为50%,约为常规分割放疗的2倍,还会导致更严重的组织水肿和口干。

2.3 辅助结构损伤

唾液在咀嚼、吞咽和味觉感知中起着至关重要的作用。辐射会导致唾液腺的腺泡细胞急性死亡,而且毛细血管损伤会导致腺体血液灌注减少以及慢性腺体萎缩,进而,唾液分泌缺乏造成的口干降低了吞咽效率,最终导致吞咽困难。放疗后,约53%的口干症患者会发生吞咽困难^[16],还有研究结果显示,降低腮腺辐射剂量可以有效改善口干症,从而降低吞咽困难的发生率^[17]。

2.4 神经损伤

吞咽过程受复杂的神经控制,肿瘤侵袭、压迫和癌症治疗均可引起支配吞咽肌和向中枢神经系统传递信息的神经受到损伤。放射性脑神经损伤(如三叉神经的损伤)会导致运动纤维支配的吞咽运动失调^[18]。周围神经损伤可导致向三叉神经核团上传的吞咽感觉中断,另外辐射损伤造成的感觉通路紊乱,可造成持续或无法控制的疼痛^[19]。手术损伤或辐射诱导的神经组织微循环改变,轴突和髓鞘薄壁组织损伤、脱髓鞘及轴索退变,也可导致神经功能障碍,最终引起吞咽困难。

另外,吞咽功能受损的患者,通常进食不畅且伴随疼痛,因此需要避免食用较硬的食物。有数据显示,水样食物会导致患者发生误吸,而糊样食物可有效消除50%的误吸,但个体对食物浓度的适应性及食物浓度对吞咽障碍的改善,还需进一步试验确认^[20]。

3 吞咽困难的评估

评估吞咽困难的方法有量表评估和影像学评估。常用的吞咽功能评估量表有安德森吞咽困难量表、悉尼吞咽问

卷、饮水试验、饮食正常度评定量表,其中安德森吞咽困难量表简单明了,悉尼吞咽问卷能够提供更详细的信息将吞咽功能分组^[21]。通常量表评估的吞咽结果与饮食限制有较强的一致性,但常低估实际吞咽困难的发生率,必须综合评估以评定患者的吞咽困难等级^[22]。

视频透视吞咽检查是评估吞咽障碍的标准影像学技术,通过可视化,并结合改良的钡剂吞咽障碍量表、穿透摄入量表、吞咽功能状态量表对视频透视吞咽检查进行评分,可以量化吞咽障碍程度^[23],另外纤维内窥镜可以直观观察到吞咽过程^[22]。Xinou等^[23]发现,无论是否存在主观吞咽困难,在放疗前和放疗后1个月、3个月进行视频透视吞咽检查,将有助于早期吞咽康复计划的实施。

头颈部肿瘤吞咽困难评估是其防治的重要环节,但临床上尚无明确评估标准,需要探寻更灵敏和便利的方法,对患者吞咽功能进行评估。

4 吞咽困难的预防和治疗措施

4.1 放疗技术的改进

Feng等^[24]采用调强放疗技术限制关键吞咽结构的辐射剂量进行口咽癌放疗,具有较高肿瘤控制率的同时降低了放疗后吞咽困难的程度。为吞咽困难-误吸相关结构的研究和控制放疗对吞咽相关器官的剂量奠定了基础,咽缩肌的受量从61~64 Gy降到52~55 Gy,吞咽困难的发生率降低30%;声门上喉受量<55 Gy,吞咽困难的发生率可降低20%。另外会厌受量限制在V60(接受 ≥ 60 Gy剂量照射的会厌体积占会厌总体积的百分比)<60%,以及颏下肌肉组织如颏舌骨肌、下颌舌骨肌的辐射总剂量 ≤ 69 Gy也对维持正常吞咽功能至关重要^[10]。

同时,中重度口干症的发生率在二维放疗时为60%~75%,采用调强放疗时降为40%^[25],而唾液腺功能在唾液腺平均辐射受量<10~15 Gy时基本正常,>40 Gy时可降低75%。目前认为,使对侧腮腺受量<26 Gy,下颌下腺受量<35 Gy,可减少口干症,进而预防吞咽困难的发生^[26]。

放疗技术及靶区优化方法的发展(如在进行吞咽困难-误吸相关结构勾画时,可融合MRI作为CT的补充)能够优化剂量分布^[27];容积调强放疗能将靶区边界从5 mm降至3 mm,结合图像引导放疗系统,可以更精确地放疗,降低放射毒性程度^[28]。Baumann等^[29]将质子与光子放疗对比,发现质子放疗可显著减少急性不良反应,并达到与光子放疗相当的疗效。另外螺旋断层放疗具有更高的剂量适形度,期待其在防护头颈部肿瘤放疗对吞咽功能损伤的应用及研究成果。

4.2 放疗不良反应的处理

有研究结果显示,黏膜保护剂能缓解吞咽疲劳,减轻

因放疗引起的急性口腔黏膜炎和吞咽困难^[30]。Dalodom等^[31]发现,患者连续4周摄入一种称为口腔保湿果冻的新型可食用唾液替代品,可显著减少口干症状,这可能有助于减少吞咽困难的发生。同时,Beadle等^[32]发现,给行调强放疗的头颈部肿瘤患者放置营养管后,其吞咽功能显著改善,该方法可以减轻患者的营养不良、脱水等情况,还可以缓解疼痛。但也有研究结果显示,预防性置管会减少咀嚼肌活动,导致吞咽肌萎缩,增加长期吞咽困难发生的风险,而维持口服摄入,避免咽部停用可能有更好的吞咽功能^[33]。另外Peng等^[34]发现,在放疗期间进行神经肌肉电刺激治疗能够防治放疗诱导的肌肉纤维化和吞咽困难。

4.3 吞咽功能训练

评估预防性或治疗性吞咽训练干预措施作用的前瞻性随机试验较少。有研究针对口腔和咽部结构进行预防性干预训练,结果显示,早期干预与晚期干预均对预防吞咽困难的发生有益,但早期干预更利于吞咽功能的恢复^[35]。另有研究结果证实,与放疗后的吞咽训练相比,放疗前训练使得患者的生活质量下降更少,吞咽困难程度更轻^[36]。然而也有研究结果显示,吞咽训练对放疗后第一年的吞咽功能没有改善^[37],这可能是吞咽训练对患者具有挑战性,在此过程中患者因吞咽不适、疼痛或误吸而终止训练,导致患者依从性差而造成的。

生存期超过2年的头颈部肿瘤患者的吞咽困难发生率为50%~60%^[6]。尽管经过放疗技术的改进、放疗不良反应的处理以及吞咽功能训练的干预,仍然只有32%的头颈部肿瘤患者的吞咽困难好转,48%的患者未能改善,且20%的患者吞咽困难加重^[38]。

5 小结与展望

吞咽困难一直是头颈部肿瘤患者放疗后的困扰,多学科联合康复计划有益于患者吞咽功能的预防及恢复,但仍然未能有效解决问题。即使最新的放疗技术可优化辐射剂量分布,吞咽系统仍无法避免受到辐射损伤,因此,还需要进一步提高肿瘤放疗的精确度,研究辐射引起的不良反应导致的吞咽困难形成的具体机制。基于靶向治疗的快速发展,Xiang等^[39]发现,放疗联合西妥昔单抗能取得与化疗联合相近的疗效,并且不会导致严重的黏膜炎发生,同时还能降低吞咽困难的发生率。因此,开发能降低放疗诱导的不良反应发生率的药物是防治吞咽困难的一个重要方向。同时,多项研究结果^[35-35]已经证明预防性吞咽功能训练有益,但吞咽功能训练最有效的干预时间、类型和强度仍然需要阐明,也需要探究合理的评估方法以及可靠易行的措施来保障吞咽功能训练的实施,以制定更有效的防治方案。

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